SAMSUNG MEDICAL CENTER

SUNG KYUN KWAN UNIVERSITY (SKKU)

증례로 살펴보는

B형간염 가이드라인과 간염치료

2016.4.6

성균관대학교 삼성서울병원 소화기내과
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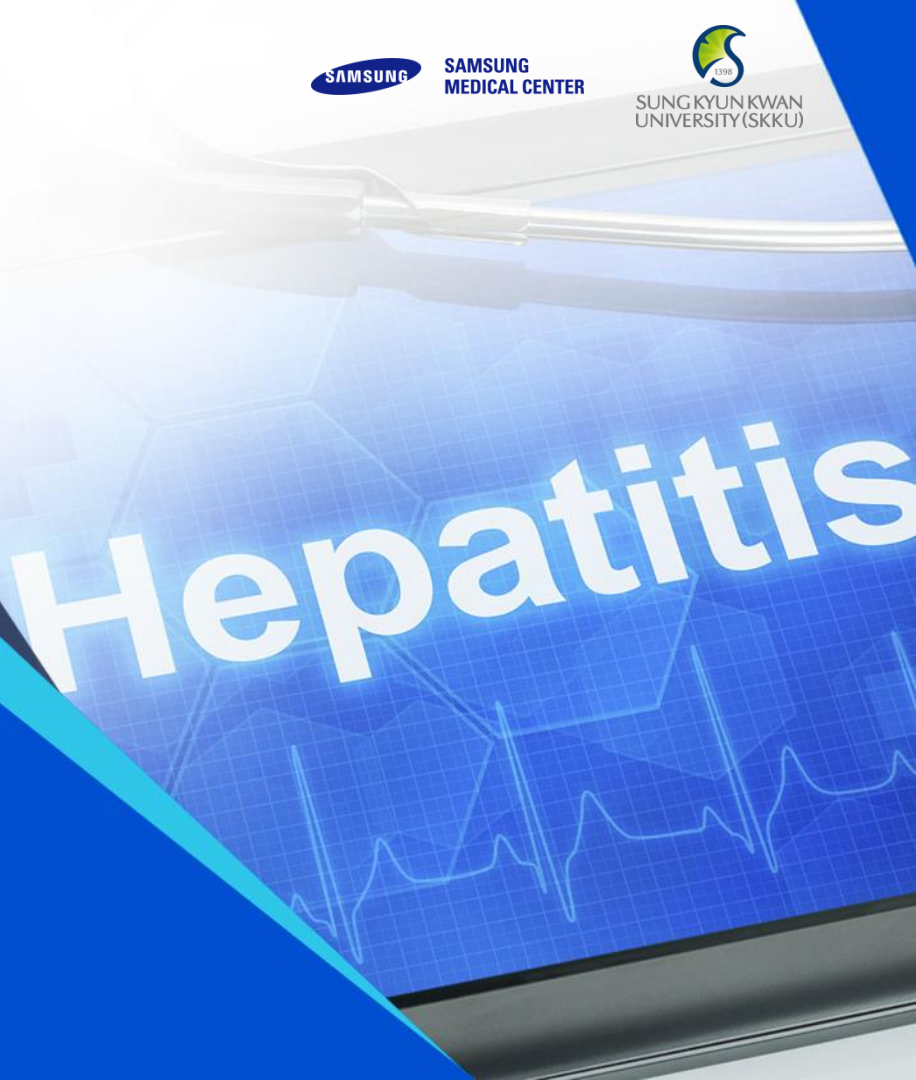
신 동 현



Today’s topic

1. HBV 가이드라인 리뷰

2. 증례 검토

What has been changed so far?

Time	1976	2016
Seoul sights		
HBV	Presence (O) Vaccination (X) Suppression of replication (X) Eradication (X)	Presence (O) Vaccination (O) Suppression of replication (O) Eradication (X)

How to decide a target group for treatment?

Cure << Control

- At risk of hepatic complications
- Treatment **proven** to reduce complications
- Benefit > Risks

What factors is associated with hepatic complications

Viral factors

- ✓ HBeAg (Hazard ratio [HR], 4.2)
- ✓ HBV DNA level > 10^4 copies/ml (HR, 2.7)
- ✓ HBV DNA level > 10^5 copies/ml (HR, 8.9 - 10.7)

Host factors

- ✓ Male gender (HR, 3.0)
- ✓ Advanced age (HR, 3.6 – 8.3)
- ✓ Alcohol consumption (HR, 2.6)
- ✓ Cigarette smoking (HR, 1.7)

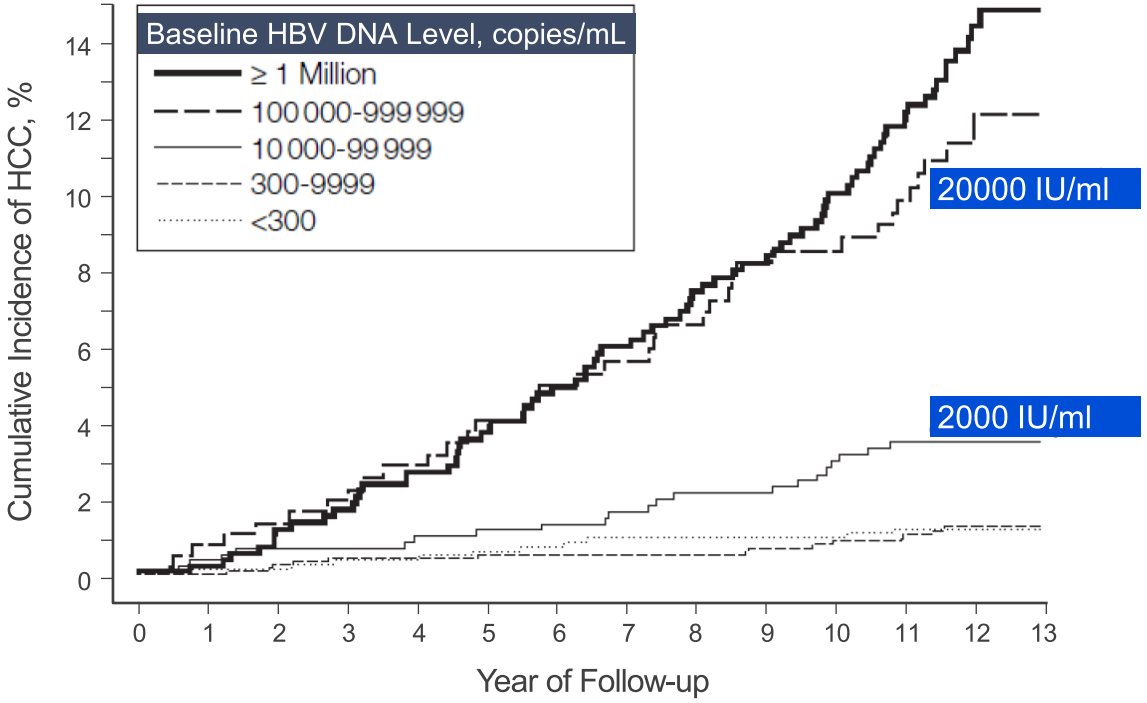
Other factors

- ✓ Severity and frequency of ALT elevations
- ✓ HCV/HDV coinfection, immunosuppression, HBV genotype C, presence of HBV precore or core promoter mutations, obesity

US Treatment algorithm, 2008

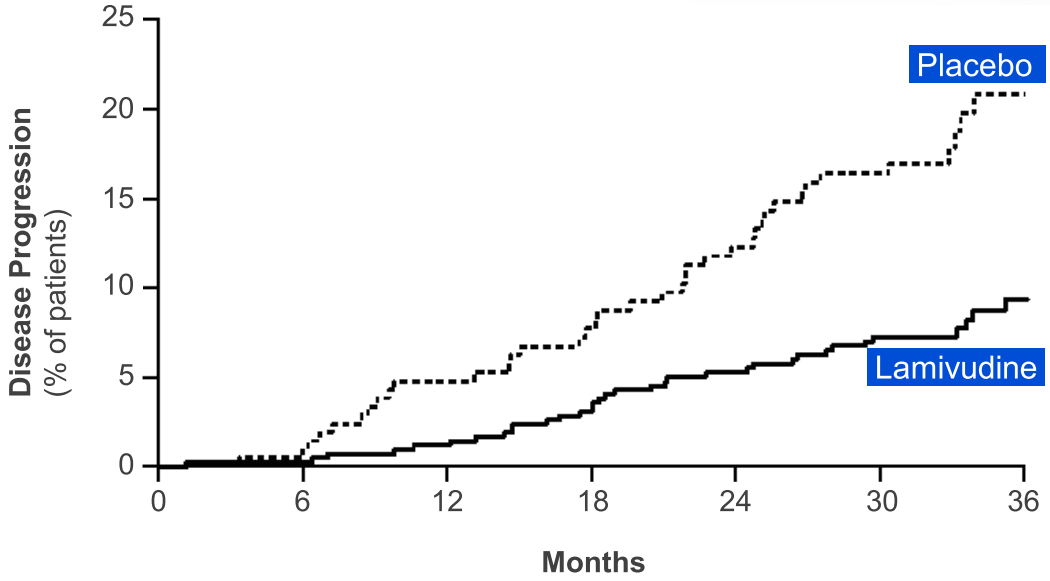
HBV DNA and HCC: **REVEAL study**

Entire Cohort (N=3653)



Chen et al., JAMA 2006;295:65

Evidence that treatment can meet the '**goal**'



No. at Risk

placebo	215	209	198	184	173	153	43
Lamivudine	436	429	417	400	385	347	122

Liaw et al, N Engl J Med 2004;351:15

Why not treat **all** CHB patients with high serum HBV DNA levels?

	Immune tolerant	HBeAg-positive CHB (immune clearance)	Immune control (low or non-replicative)	HBeAg-negative CHB (immune escape)
HBeAg	**Positive** (2000-5000 PEIU/ml)	**Positive** (100-1000 PEIU/ml)	**Negative**	**Negative**
Anti-HBe				
HBsAg(log IU/ml)	**4.5-5**	**4.0-4.5**	**2.9-3.0**	**3.3-3.9**
Anti-HBs				
HBV DNA(IU/ml)	**>20000**	**>20000**	**<2000**	**>2000**
Viral diversity (PC/C ORF)				
Serum ALT level (U/l)	Persistently nomal	Elevated(1-2X) and fluctuating	Normal	Elevated and fluctuating
Liver histology	Normal or mild hepatitis	Moderate to severe hepatitis	Normal to mild hepatitis. May have cirrhosis	Moderate to severe hepatitis. May have cirrhosis
Intra-hepatic HBV replicative, intermediates	rcDNA/cccDNA (100-1000) >1 cccDNA/cell	rcDNA/cccDNA (10-1000) 1 cccDNA/cell (0.1-10/cell)	rcDNA/cccDNA (10-100) 0.1 cccDNA/cell (0.001-1/cell)	rcDNA/cccDNA (100-1000) >1 cccDNA/cell (0.1-10/cell)

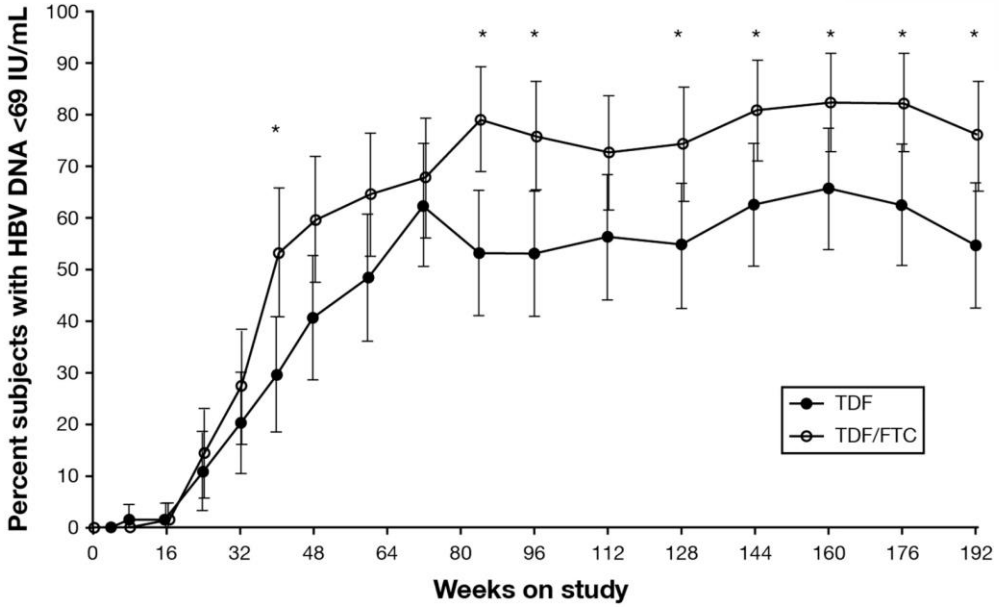
Normal or

mild hepatitis in

immune tolerant phase

Dandri M , Locarnini S Gut 2012;61:i66

Effects of TDF on HBe (e+) with High viral load and normal ALT levels



TDF	N=64	61	62	62	62	61	60	59	58	57	55	55	53	53
TDF/FTC	N=62	61	60	58	57	57	57	56	57	56	56	55	55	54

*P<.05

Chan HL et al., Gastroenterology 2014;146:1240

Effects of AVT in patients with low viremia

No data yet.

However, generally, patients has very favorable prognosis when they are in “inactive carrier state”.

Key concept

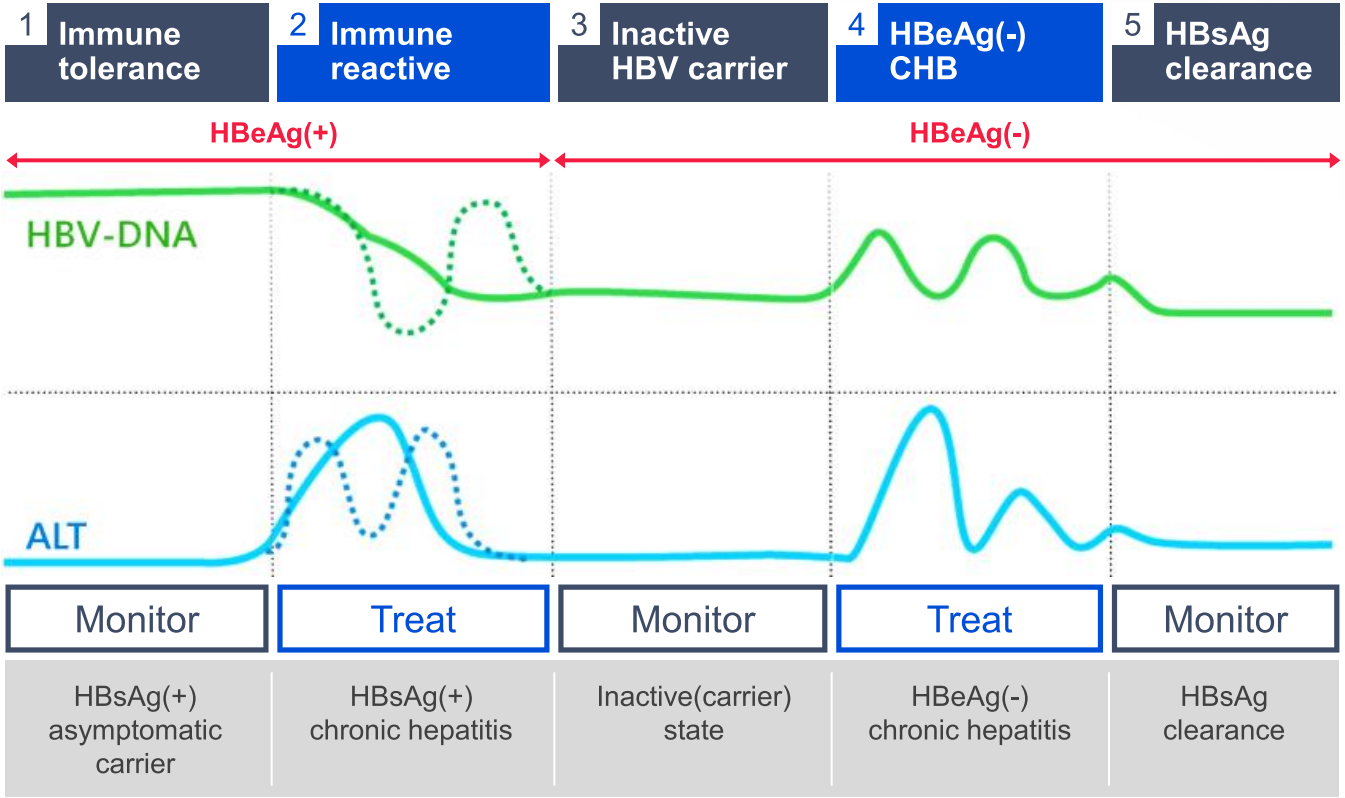
01 In immune tolerance phase and inactive carrier phase, there is a minimal risk of disease progression.

02 There is no effective treatment that has proven benefit in this setting.

03 In these two phases, treatment is generally not recommended.

How can I know CHB phase in individual patient?

Disease course of **CHB**



Immune tolerance vs. clearance

Similarities: HBeAg+, high DNA

Immune tolerance phase

- ✓ Most are under 30 years of age
- ✓ Persistently normal ALT level
- ✓ Usually very high HBV DNA level

(No suspicion of advanced disease in radiologic evaluation)

Immune clearance phase

- ✓ Fluctuating ALT level
- ✓ Fluctuating DNA level

Inactive carrier vs. immune reactivation

Similarities: HBeAg negative

Inactive carrier

- ✓ Low level of HBV DNA (< 2,000 IU/mL)
- ✓ Normal ALT
- ✓ HBeAg/anti-Hbe (-/+)
- ✓ Low level of quantitative HBsAg (< 1,000 IU/mL)

Immune reactivation phase

- ✓ Fluctuating ALT
- ✓ Fluctuating HBV DNA

Key concept

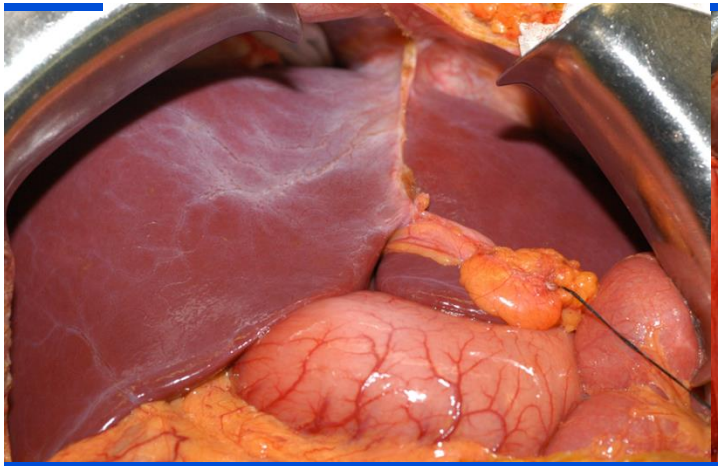
By adding ALT & HBV DNA levels as an indicator for treatment initiation,

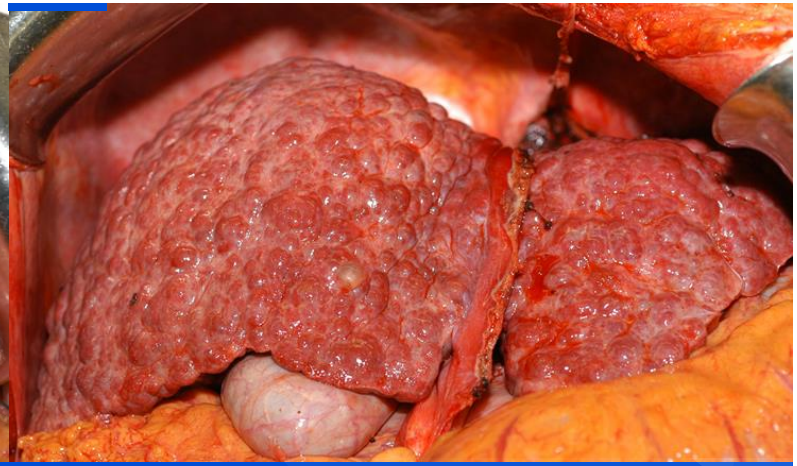
one can distinguish CHB phase, that requires therapy

Treatment criteria for **CHB**

Liver disease severity	Liver society	HBV DNA, IU/mL	ALT
Chronic hepatitis	EASL, 2012	≥ 2,000	≥ ULN
	AASLD, 2015	≥ 20,000 (e+), ≥ 2,000 (e-)	≥ 2 X ULN
	KASL, 2015	≥ 20,000 (e+), ≥ 2,000 (e-)	≥ 2 X ULN

Cirrhosis





The levels of AST/ALT **should not be used** as criteria for starting antiviral therapy in patients with liver cirrhosis

- ✓ They already have significant hepatic fibrosis
- ✓ They frequently have nearly normal AST/ALT levels.

2015 KASL guideline for chronic hepatitis B

Limited role of ALT in cirrhosis patients

Hepatocellular Carcinoma Risk of Compensated Cirrhosis Patients with Elevated HBV DNA Levels according to Serum Aminotransferase Levels

Junggyu Lee,[1*] Dong Hyun Sinn,[1*] Jung Hee Kim,[1] Geum-Youn Gwak,[1] Hye Seung Kim,[2] Sin-Ho Jung,[2] Yong-Han Paik,[1] Moon Seok Choi,[1] Joon Hyeok Lee,[1] Kwang Cheol Koh,[1] Byung Chul Yoo,[1] and Seung Woon Paik[1]

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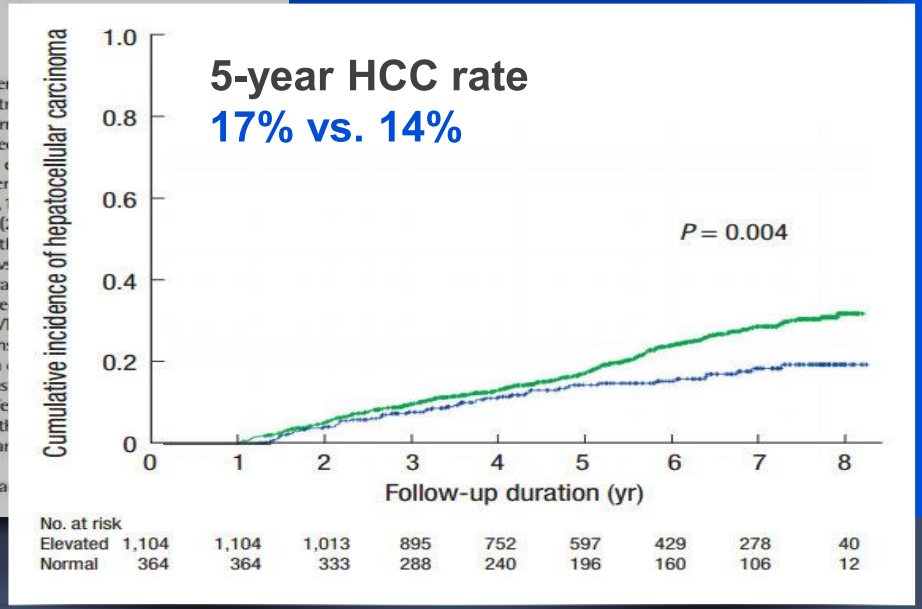
Sometimes, hepatitis B virus (HBV)-related cirrhotic patie
levels are closely followed-up for the elevation of aminotr
prompt antiviral therapy (AVT). We analyzed the long-ter
risk according to the aminotransferase levels in a retrospe
naïve, HBV-related, compensated cirrhosis patients with
(≥ 2,000 IU/mL). Based on aminotransferase levels, patie
(< 40 U/L, n = 364) and elevated group (≥ 40 U/L, n = 1,
of follow-up (range: 1.0-8.2 yr), HCC developed in 296 (
cumulative HCC incidence rate was higher in patients wit
but was not low in normal aminotransferase level (17% v
follow-up, 270/364 (74%) patients with normal aminotra
elevation of aminotransferase levels, and AVT was initiate
patients with normal aminotransferase levels received AV
median time to start AVT was longer (17.9 vs. 2.4 month
an independent factor associated with HCC, and median
vs. 2.6 yr, $P < 0.001$) in patients with normal aminotrans
compensated cirrhosis patients with normal aminotransfe
duration is associated with lowered HCC risk, indicating t
strongly considered even for those with normal aminotra

Keywords: Liver Neoplasms; Antiviral Therapy; Aminotra



J Korean Med Sci 2015;30:1618

Compensated cirrhosis patients with low viremia

65/M

- Alleged chronic hepatitis B
- No treatment history of chronic hepatitis B

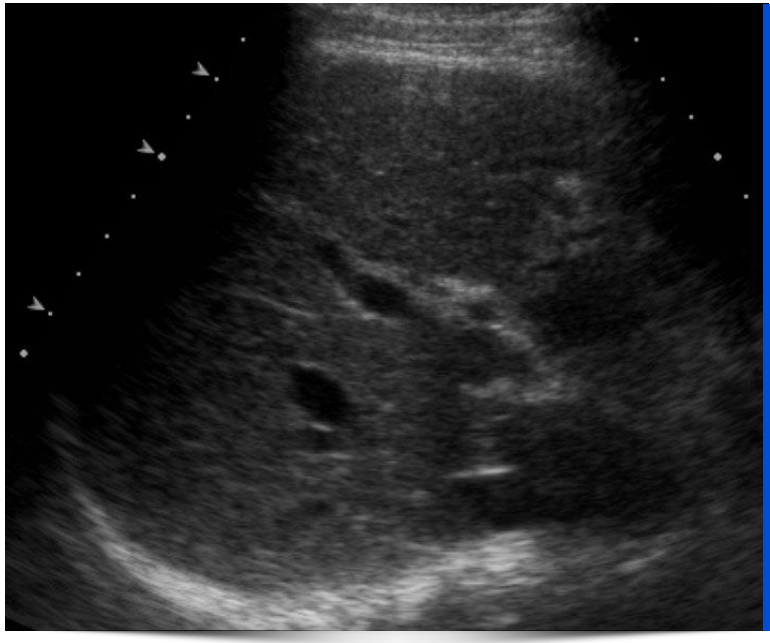
- Past medical history: Hypertension diagnosed 1 year ago, and taking medication
- Social history: alcohol – social, smoking - none
- Family history: HBV (+), HCC (-)

- ROS: asymptomatic
- PE: nonspecific

Clinical course

- 2008. 3

- ✓ CBC: 4850-14.0- **125k**
- ✓ PT: 1.10 INR
- ✓ Albumin: 4.0 g/dl
- ✓ Bilirubin = 1.0 mg/dl
- ✓ AST/ALT: 30/17 U/L
- ✓ AFP: 2.2 ng/ml
- ✓ HBV DNA: **39 IU/mL**
- ✓ HBeAg (-) HBeAb (+)
- ✓ US: coarse echotexture

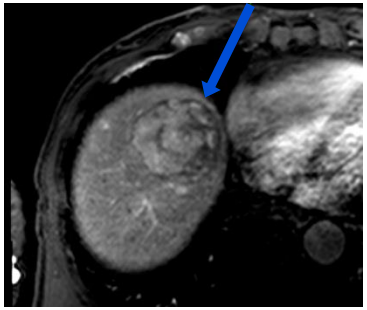


What is your next choice?

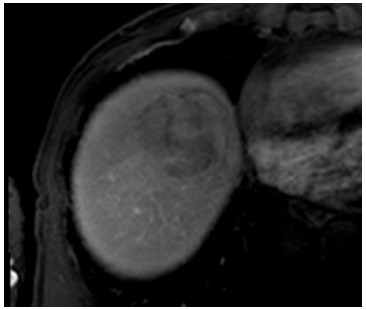
Clinical course

● 2012. 6

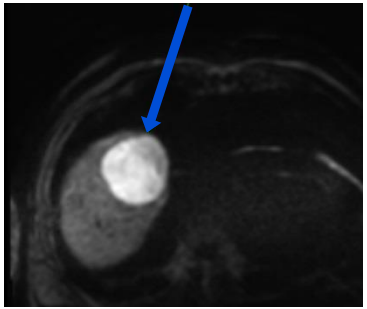
Arterial



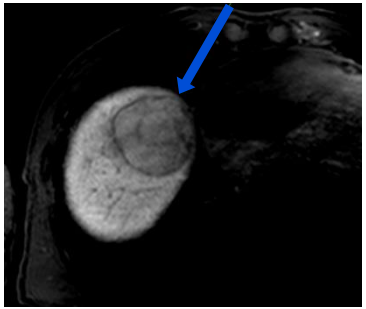
Delay



Diffusion

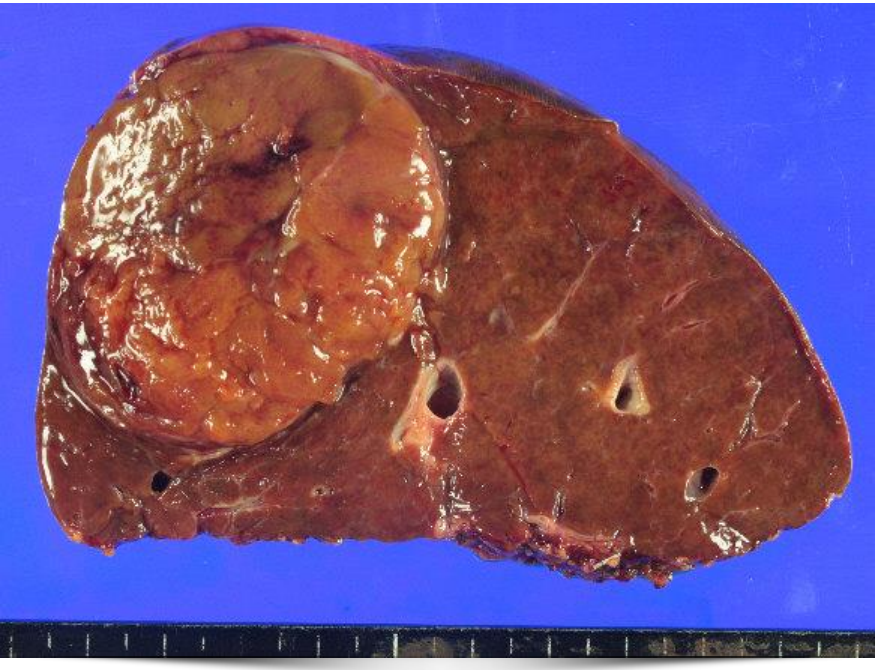


Hepatobiliary



- ✓ CBC: 4020-13.2- **99k**
- ✓ PT: 1.09 INR
- ✓ Albumin: 4.6 g/dl
- ✓ Bilirubin = 0.8 mg/dl
- ✓ AST/ALT: 24/10 U/L
- ✓ AFP: 2.6 ng/ml
- ✓ HBV DNA: **83 IU/mL**
- ✓ HBeAg (-) HBeAb (+)

Resection (segmentectomy)



Progressed hepatocellular carcinoma, S4/8:

Gross type : Simple nodular type with extranodular growth

Differentiation : Edmondson grade II > I

Histologic type : pseudoglandular

Cell type : hepatic

Tumor size : 5.5x4.7x4 cm

Tumor number : one

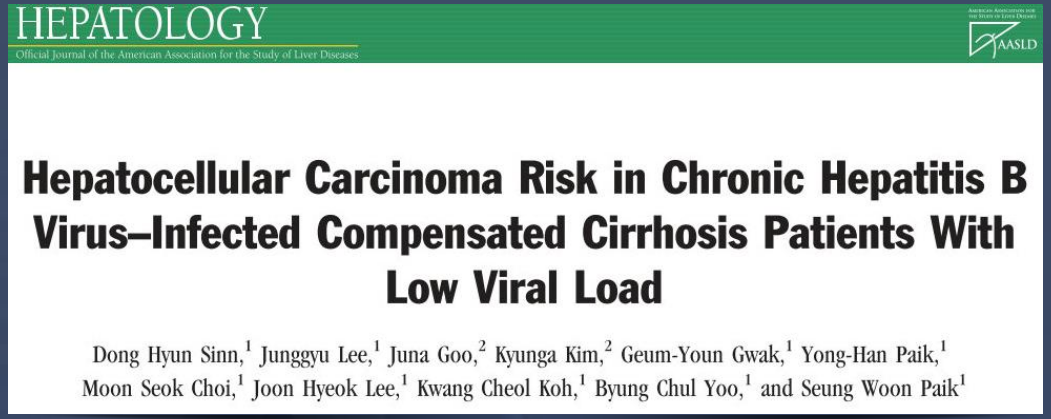
Fatty change : no

Microvessel invasion : no

Intrahepatic metastasis (satellite nodule) : no

Multicentric occurrence : no

Surgical margin invasion : no (safety margin : 1 cm)



HEPATOLOGY
Official Journal of the American Association for the Study of Liver Diseases
AASLD

Hepatocellular Carcinoma Risk in Chronic Hepatitis B Virus–Infected Compensated Cirrhosis Patients With Low Viral Load

Dong Hyun Sinn,[1] Junggyu Lee,[1] Juna Goo,[2] Kyunga Kim,[2] Geum-Youn Gwak,[1] Yong-Han Paik,[1] Moon Seok Choi,[1] Joon Hyeok Lee,[1] Kwang Cheol Koh,[1] Byung Chul Yoo,[1] and Seung Woon Paik[1]

A retrospective cohort of 385, treatment-naïve, HBV-related compensated cirrhosis patients at Samsung Medical Center

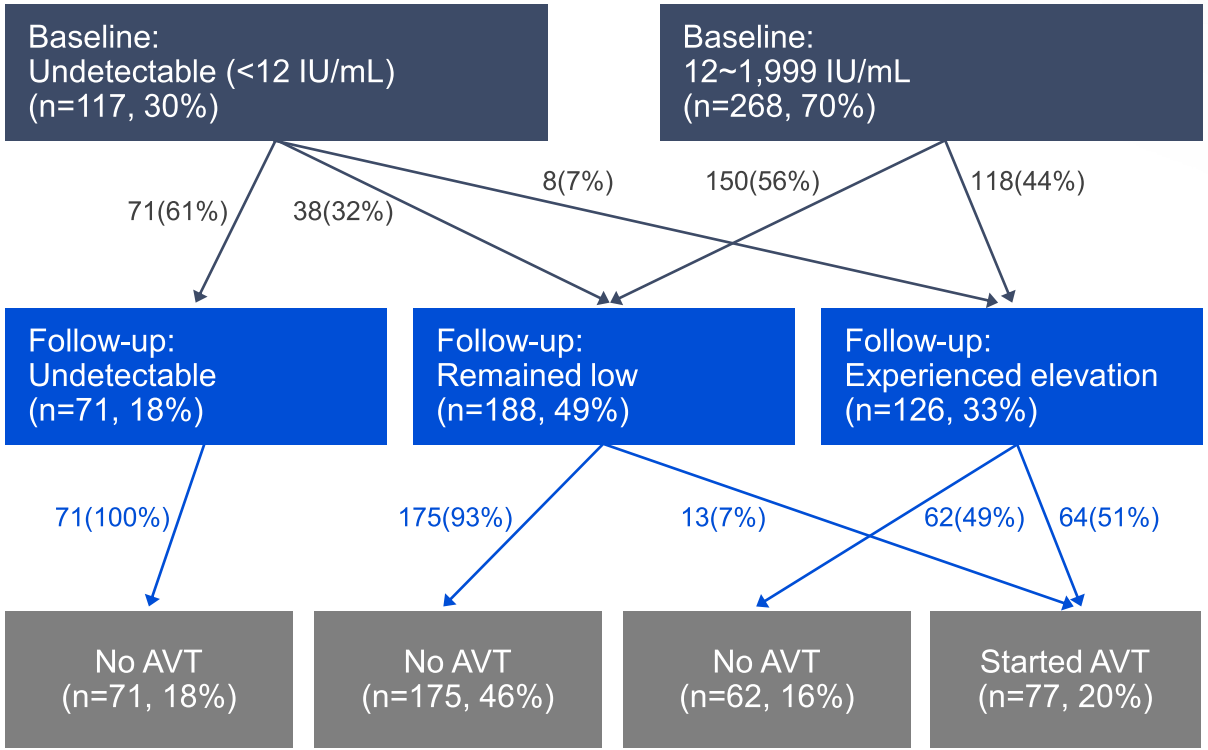
- ✓ Age: 51.1 ± 9.7 years
- ✓ Male: 66%
- ✓ Median follow-up: 5.6 years
- ✓ HCC: 37 patients (9.6%)

Baseline characteristics

Characteristics	All (n=385)	No HCC (n=348)	HCC (n=37)	*P* Value	No AVT (n=308)	AVT (n=77)	*P* Value
Age, years, mean ± SD	51.1 ± 9.7	50.7 ± 9.5	55.3 ± 10.4	0.006	51.8 ± 9.8	48.3 ± 9.0	0.005
Male, n (%)	252 (66)	228 (66)	24 (65)	0.93	202 (66)	50 (65)	0.91
HBeAg positive, n (%)	37 (10)	15 (4)	3 (8)	0.29	11 (4)	7 (9)	0.063
Cirrhosis, n (%)							
Thrombocytopenia (<150 × 10^3/μL)	329 (86)	298 (86)	31 (84)	0.76	266 (86)	63 (82)	0.31
Radiological findings*	204 (53)	184 (53)	20 (54)	0.89	154 (50)	50 (65)	0.019
Varices†	77 (27)	68 (26)	9 (32)	0.47	62 (27)	15 (25)	0.71
Child-Pugh score (%)				0.40			0.93
5	346 (90)	314 (90)	32 (87)		277 (90)	69 (90)	
6	39 (10)	34 (10)	5 (13)		31 (10)	8 (10)	
ALT, U/L, median (quartile)	25 (18-36)	25 (18-35)	28 (21-39)	0.27	24 (18-34)	30 (23-43)	0.001
Elevated ALT (%)	130 (34)	115 (33)	15 (41)	0.35	95 (31)	35 (46)	0.015
AST, U/L, median (quartile)	28 (22-36)	28 (22-25)	31 (25-41)	0.028	28 (22-34)	31 (25-39)	0.007
Albumin, mg/dL, median (quartile)	4.2 (4.0-4.4)	4.2 (4.1-4.4)	4.1 (3.9-4.4)	0.14	4.2 (4.0-4.4)	4.2 (4.0-4.3)	0.15
Bilirubin, mg/dL, median (quartile)	1.0 (0.7-1.3)	1.0 (0.7-1.3)	1.0 (0.7-1.2)	0.42	1.0 (0.7-1.3)	1.0 (0.7-1.3)	0.99
Platelet, ×10^3/μL, median (quartile)	127 (100-145)	128 (101-145)	119 (91-144)	0.20	129 (102-145)	120 (95-143)	0.10
AFP, ng/mL, median (quartile)‡	3.2 (2.4-5.2)	3.2 (2.4-4.9)	3.8 (2.7-8.5)	0.028	3.1 (2.4-4.8)	3.8 (2.7-6.5)	0.003
HBV-DNA levels at baseline				0.006			<0.001
Undetectable, <12 IU/mL (%)	117 (30)	113 (32)	4 (11)		113 (37)	4 (5)	
Low viral load, 12~1,999 IU/mL (%)	268 (70)	235 (68)	33 (89)		195 (63)	73 (95)	
HBV-DNA levels during follow-up (%)				0.091			<0.001
Remained undetectable	71 (18)	69 (20)	2 (5)		71 (23)	–	
Remained low viral load	188 (49)	166 (48)	22 (60)		175 (57)	13 (17)	
Experienced elevation (≥2,000 IU/mL)	126 (33)	113 (32)	13 (35)		62 (20)	64 (83)	

Hepatology 2015;62:694

Flow diagram of patients by HBV DNA levels



Hepatology 2015;62:694

Baseline risk factors for HCC development

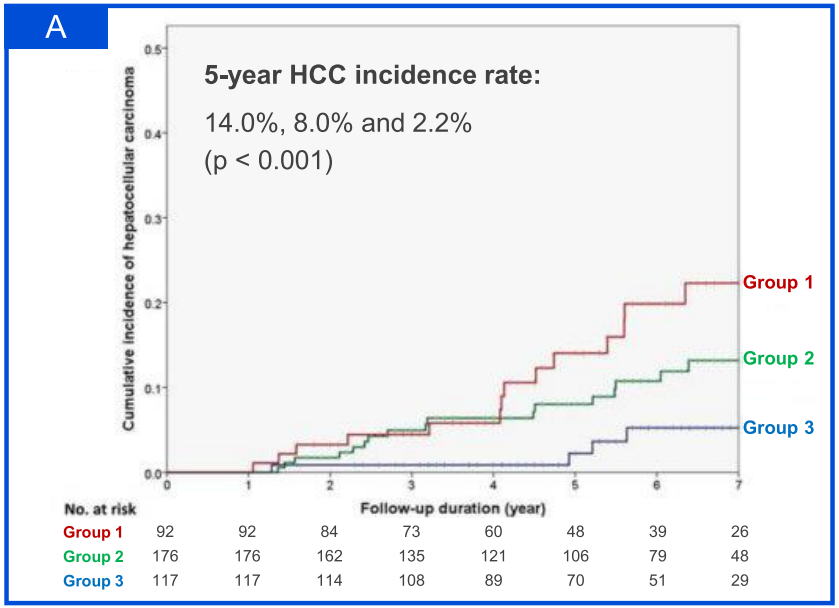
Baseline Factor	All (n=385)				Patients Without AVT During Follow-up (n=308)			
	Univariate		Multivariate		Univariate		Multivariate	
	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value	HR (95% CI)	*P* Value
Age (/year)	1.05 (1.02-1.09)	0.004	1.06 (1.02-1.10)	0.002	1.03 (0.99-1.07)	0.074	1.04 (1.01-1.08)	0.045
Male (vs. female)	0.96 (0.49-1.89)	0.91			0.83 (0.39-1.75)	0.63		
HBeAg (+)	1.83 (0.56-6.00)	0.31			2.53 (0.60-10.6)	0.20		
Child score (6 vs. 5)	1.44 (0.56-3.71)	0.44			1.46 (0.51-4.21)	0.47		
ALT (/IU/mL)	1.01 (1.01-1.02)	0.010	1.01 (0.99-1.02)	0.34	1.01 (1.01-1.02)	0.001	1.01 (0.99-1.02)	0.20
AST (/IU/mL)	1.02 (1.01-1.04)	<0.001	1.01 (0.98-1.03)	0.35	1.03 (1.01-1.04)	<0.001	1.01 (0.98-1.03)	0.34
Albumin (/mg/dL)	0.35 (0.13-0.93)	0.036	0.71 (0.21-2.37)	0.58	0.24 (0.09-0.65)	0.005	0.36 (0.10-1.26)	0.11
Bilirubin (/mg/dL)	0.60 (0.29-1.23)	0.16			0.52 (0.23-1.20)	0.12		
Platelet (/$\times 10^3$/μL)	0.99 (0.99-1.01)	0.57			0.99 (0.99-1.01)	0.66		
AFP (/ng/mL)	1.01 (1.00-1.01)	<0.001	1.01 (1.00-1.01)	<0.001	1.01 (1.00-1.01)	<0.001	1.01 (1.00-1.01)	<0.001
Detectable HBV DNA (vs. undetectable)	3.84 (1.36-10.8)	0.011	5.20 (1.53-17.6)	0.008	4.18 (1.46-11.9)	0.008	5.90 (1.66-20.9)	0.006
Normal ALT*	3.32 (1.13-9.77)	0.029	5.52 (1.46-20.7)	0.011	3.08 (1.01-9.37)	0.047	4.74 (1.22-18.4)	0.025
Elevated ALT*	4.88 (1.60-14.8)	0.005	4.99 (1.38-18.0)	0.014	7.16 (2.30-22.2)	0.001	6.98 (1.90-25.6)	0.003

* Adjusted model included age, ALT, AST, albumin, AFP, and HBV-DNA levels.
Elevated ALT is defined for ≥34 IU/L for men and ≥25 IU/L for women.

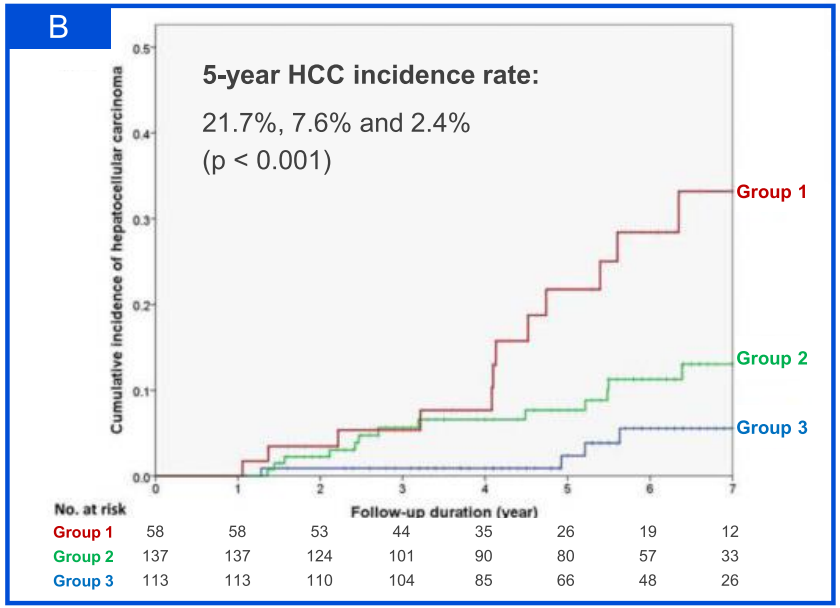
Hepatology 2015;62:694

Risk of HCC during follow-up

All patients
(n = 385)



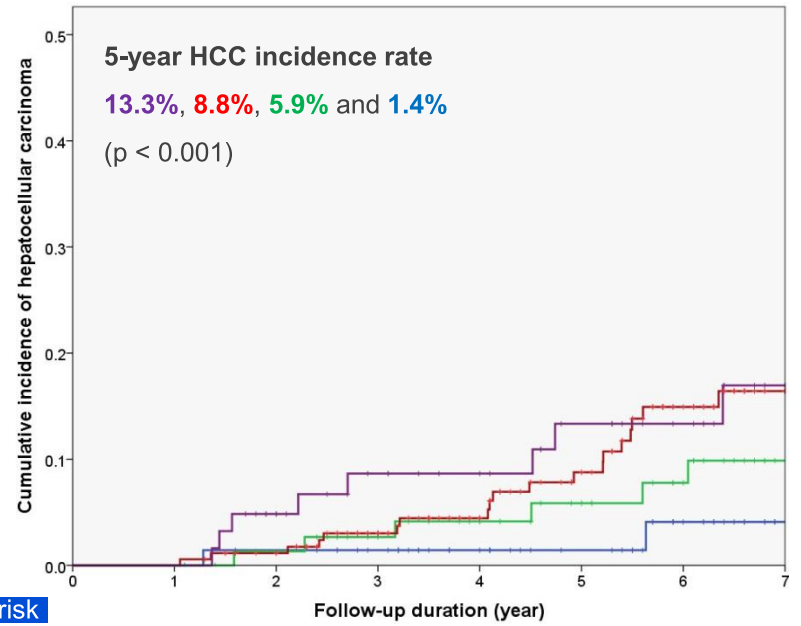
Patients without antiviral therapy during follow-up
(n = 308)



Group 1: patients with low HBV DNA levels plus elevated ALT levels
Group 2: patients with low HBV DNA levels plus normal ALT levels
Group 3: patients with undetectable HBV DNA levels (< 12 IU/ml)

Sinn DH et al., Hepatology 2015; 62:694

HCC risk by change in HBV DNA levels during follow-up



No. at risk

Elevation	62	62	54	46	41	35	28	18
Low	175	175	165	141	118	95	66	36
Undetect	71	71	68	63	50	43	30	18
AVT	77	77	73	66	60	52	44	32

Table 4. Impact of AVT on the Development of HCC

	All (n = 385)		Patients With Detectable HBV DNA at Baseline (n = 268)	
	Estimate* (95% CI)	*P* Value	Estimate* (95% CI)	*P* Value
AVT duration	−0.22 (−0.43~−0.01)	0.038	−0.29 (−0.51~−0.08)	0.008
CVR duration	−0.34 (−0.61~−0.06)	0.018	−0.42 (−0.71~−0.12)	0.005

*Marginal structural Cox's proportional hazard model, which included age, peak HBV-DNA levels, and AVT duration or CVT duration was used to estimate impact of AVT. Detailed information for the model is shown in Supporting Tables 2-5.

Abbreviation: CI, confidence interval.

HBV DNA Elevation over 2000 U/L
Remained low viremia

Started antiviral therapy

Remained Undetectable HBV DNA

Sinn DH et al., Hepatology 2015; 62:694

Summary

Limitation: retrospective cohort, time to start AVT is different

Findings

- ✓ Higher HCC risk of low viremic patients than those with undetectable HBV DNA levels.
- ✓ Patients with detectable but low viral load experienced HBV DNA elevation frequently.
- ✓ The risk of HCC was not low even if HBV DNA levels maintained at low levels for a long time.
- ✓ AVT or CVR duration was closely associated with reduced HCC risk.

Prompt AVT is better approach than monitoring

Hepatology 2015;62:694

Recommendation by international guidelines

2015 AASLD guideline

The AASLD suggests that adults with compensated cirrhosis and low levels of viremia (<2,000 IU/mL) be treated with antiviral therapy to reduce the risk of decompensation, regardless of ALT level.

Quality/Certainly of Evidence: Very Low

Strength of Recommendation: Conditional

Recommendation by international guidelines

2015 KASL guideline

Antiviral therapy can be considered when HBV DNA is

HBV DNA is <2,000 IU/mL to reduce the risk of decompensation

regardless of AST/ALT levels for compensated cirrhosis patients. (C1)

Treatment criteria for **CHB**

Liver disease severity	Liver society	HBV DNA, IU/mL	ALT
Chronic hepatitis	EASL, 2012	≥ 2,000	≥ ULN
	AASLD, 2015	≥ 20,000 (e+), ≥ 2,000 (e-)	≥ 2 X ULN
	KASL, 2015	≥ 20,000 (e+), ≥ 2,000 (e-)	≥ 2 X ULN
Compensated cirrhosis	EASL, 2012	Detectable	Any
	AASLD, 2015	Detectable	Any
	KASL, 2015	≥ 2,000*	Any

**Treatment can be considered for those with < 2,000 IU/mL*

Definition of decompensation

Compensated cirrhosis

Decompensated cirrhosis

- ✓ Cirrhosis, complicated with ascites, variceal bleeding, hepatic encephalopathy or jaundice.
- ✓ Limited reserve.

2015 KASL guideline for chronic hepatitis B

Treatment criteria for **CHB**

Liver disease severity	Liver society	HBV DNA, IU/mL	ALT
Chronic hepatitis	EASL, 2012	≥ 2,000	≥ ULN
	AASLD, 2015	≥ 20,000 (e+), ≥ 2,000 (e-)	≥ 2 X ULN
	KASL, 2015	≥ 20,000 (e+), ≥ 2,000 (e-)	≥ 2 X ULN
Compensated cirrhosis	EASL, 2012	Detectable	Any
	AASLD, 2015	Detectable	Any
	KASL, 2015	≥ 2,000*	Any
Decompensated cirrhosis	EASL, 2012	Detectable	Any
	AASLD, 2015	Detectable	Any
	KASL, 2015	Detectable	Any

**Treatment can be considered for those with < 2,000 IU/mL*

B형간염 바이러스 농도 높고, 간수치도 높은 경우

39/M

- B형간염, 수직감염(엄마+)
- Ht = 165cm, Wt = 72kg (BMI = 26.4)
- HBeAg+
- HBV DNA = 12,590,000 IU/ml
- AST/ALT = 78/120
- US: chronic liver disease

Why we sometime don’t treat immediately?

For those with high HBV DNA levels and elevated ALT levels?

2015 KASL recommendation

HBeAg positive CHB patients with HBV DNA ≥ 20,000 IU/ mL, plus serum AST or ALT ≥ 2 ULN or significant histologic changes such as inflammation or fibrosis (≥ moderate necroinflammation; ≥ periportal fibrosis) on biopsy should be considered for treatment. (A1)

Treatment can be delayed for 3–6 months if spontaneous HBeAg seroconversion is expected. (B2)

However, patients with apparent or anticipated liver failure (i.e., those with jaundice, prolonged PT, hepatic encephalopathy, and ascites) should be treated promptly. (B1)

Advantages and disadvantages of **“Wait & See”**

01 Naturally, some patients move to “**immune control**” state.

02 Not predictable

03 Risk of disease progression during wait !

Predictive factors for early HBeAg seroconversion

Number of favorable predictors	Early HBeAg seroconversion (%)
0	3/27 (11%)
1	27/71 (38%)
2	9/12 (75%)

Favorable predictors:
nonvertical transmission, low serm HBV DNA level (<7 log copies/ml)

Kim et al, Gastroenterology 2009;136:505

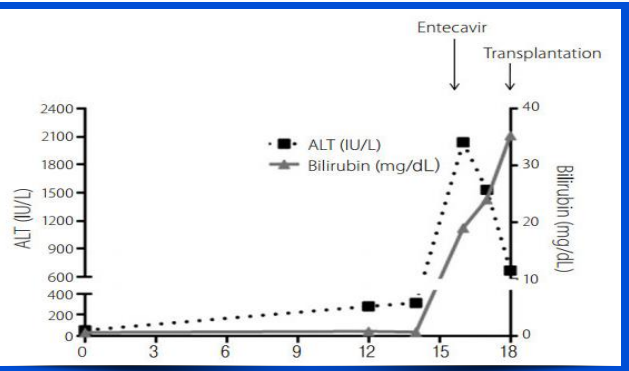
Original Article

http://dx.doi.org/10.3350/cmh.2014.20.4.355
Clinical and Molecular Hepatology 2014;20:355-360

Is it necessary to delay antiviral therapy for 3–6 months to anticipate HBeAg seroconversion in patients with HBeAg-positive chronic hepatitis B in endemic areas of HBV genotype C?

Byung-Cheol Song, Yoo-Kyung Cho, Hyeyoung Jwa, Eun Kwang Choi, Heung Up Kim, Hyun Joo Song, Soo-Young Na, Sun-Jin Boo, and Seung Uk Jeong

Department of Internal Medicine, Jeju National University School of Medicine, Jeju, Korea



Methods: Ninety patients with HBeAg-positive CHB were followed prospectively without administering antiviral therapy for 6 months. Antiviral therapy was initiated promptly at any time if there was any evidence of biochemical (i.e., acute exacerbation of HBV infection or aggravation of jaundice) or symptomatic deterioration. After 6 months of observation, antiviral therapy was initiated according to the patient's ALT and HBV DNA levels.

Results: Only one patient (1.1%) achieved spontaneous HBeAg seroconversion. Biochemical and symptomatic deterioration occurred before 6 months in 17 patients (18.9%) and 5 patients, respectively. High ALT and HBV DNA levels were both independent risk factors for biochemical deterioration. Of 15 patients with HBV DNA $\geq 5.1\times10^{7}$ IU/mL and ALT $\geq 5\times$ULN, biochemical deterioration occurred in 7 (46.7%), including 1 patient receiving liver transplantation due to liver failure.

Conclusions: Spontaneous HBeAg seroconversion in patients with HBeAg-positive CHB is rare within 6 months. Biochemical deterioration was common and may lead to liver failure. Immediate antiviral therapy should be considered, especially in patients with high ALT and HBV DNA levels in endemic areas of genotype C infection. **(Clin Mol Hepatol 2014;20:355-360)**

B형간염 바이러스 농도 높고, 간수치도 높은 경우

39/M

- B형간염, 수직감염(엄마+)
- Ht = 165cm, Wt = 72kg (BMI = 26.4)
- HBeAg+
- HBV DNA = 12,590,000 IU/ml
- AST/ALT = 78/120
- US: chronic liver disease

My choice: Prompt therapy

B형간염 바이러스 농도 높은 HBeAb 양성 환자

51/M

- B형간염
- HBeAg- HBeAb+
- HBV DNA = 890,000 IU/ml
- AST/ALT = 78/98
- US: chronic liver disease

01 이 사람은 자연적으로 DNA가 감소하여 inactive carrier로 될 수 있지 않을까?

02 관찰하는 것이 좋을까? 아니면 그냥 빨리 치료하는 것이 좋을까?

What about HBeAg negative patients?

✓ 527 HBeAg negative patients with elevated HBV DNA levels (≥ 2,000 IU/ml), followed-up SMC

Table 1. Baseline characteristics and follow-up data

Characteristics	All (n=527)	Cirrhosis (+) (n=218)	Cirrhosis (-) (n=309)	P value
Baseline characteristics				
Age (years)	48.8±9.9	51.5±8.7	46.8±10.2	<0.001
Male (n. %)	311 (59.0)	141(64.7)	170(55.0)	0.03
AST (U/L)	34 (25-54)	43(30-63)	29(23-47)	<0.001
ALT (U/L)	37 (24-66)	40(27-69)	34(22-63)	0.01
Albumin (mg/dl)	4.4 (4.1-4.6)	4.3(3.9-4.5)	4.5(4.3-4.7)	<0.001
Bilirubin (mg/dl)	0.8(0.6-1.1)	0.9(0.7-1.2)	0.8(0.6-1.0)	<0.001
PT (INR)	1.0(1.0-1.1)	1.1(1.0-1.2)	1.0(1.0-1.1)	<0.001
Platelet (x 10^3/L)	168(128-210)	118(94-138)	199(173-229)	<0.001
HBV DNA (log_{10}IU/ml)	4.9±1.2	5.1±1.3	4.7±1.1	<0.001
qHBsAg (log_{10}IU/ml)	3.3±0.6	3.2±0.6	3.4±0.6	<0.001
Follow-up data				
AVT during follow-up (n, %)	311(59.0)	175(80.3)	136(44.0)	<0.001
Disease progression (n, %)	46(8.7)	39(17.9)	7(2.3)	<0.001
HCC	40(7.6)	33(15.1)	7(2.3)	<0.001
Cirrhotic complication	6(1.1)	6(2.8)	0(0)	0.01
Inactive carrier (n,%)	31(5.9)		31(10.0)	

Sinn DH et al., PLOSone 2015;10:e0144777

What about HBeAg negative patients?

Groups	Disease progression			Inactive carrier		
	Person-years of follow-up	3year	5year	Person-years of follow-up	3year	5year
Age < 50 years(n=180)						
Group A (n=38)	155	0%	0%	119	25.1%	39.5%
Group B (n=45)	172	0%	0%	163	10.1%	10.1%
Group C (n=35)	133	4.2%	4.2%	131	3.8%	7.9%
Group D (n=62)	238	1.8%	1.8%	241	0%	0%
Age > 50 years(n=129)						
Group A (n=36)	121	3.6%	3.6%	108	13.1%	42.2%
Group B (n=30)	107	3.6%	3.6%	93	17.5%	17.5%
Group C (n=32)	113	5.6%	5.6%	113	0%	0%
Group D (n=31)	104	3.4%	3.4%	108	0%	0%

Group	**HBV DNA** (IU/mL)	**qHBsAg** (IU/mL)
A	<20,000	<2,500
B	<20,000	≥2,500
C	≥20,000	<2,500
D	≥20,000	≥2,500

Key message

Don’t wait too long for older patients
HBV DNA & qHBsAg can risk-stratify treatment policy

Sinn DH et al., PLOSone 2015;10:e0144777

B형간염 바이러스 농도 높은 HBeAb 양성 환자

51/M

- B형간염
- HBeAg- HBeAb+
- HBV DNA = 890,000 IU/ml
- AST/ALT = 78/98
- US: chronic liver disease

My choice:
Prompt therapy

Summary

Determine severity of liver disease and CHB phase

Hepatitis

ALT 상승된 사람은 **“immune control status”** 진행될 가능성을 살펴보아,
높지 않으면 바로 치료 시작

- HBeAg (+) HBV DNA,transmission mode
- HBeAg (-) Age, HBV DNA, qHBsAg

ALT 정상 또는 경미하게 상승된 사람은?

CASE

48/M

- B형간염
- HBeAg+
- HBV DNA = 2,090,000 IU/mL
- AST/ALT = 38/26
- US: chronic liver disease

Study design, setting and participants

- ✓ Derivation cohort (n = 971, Samsung Medical Center)
- ✓ Validation cohort (n = 507, Seoul National University Hospital)

Inclusion criteria

01	aged 18 years or older
02	chronic HBV infection (HBsAg + for 6 months or clinical history)
03	No evidence of any of the following clinical indicators of cirrhosis
04	**Serum HBV DNA ≥ 2000 IU/ml** at the baseline
05	No previous history or current use of antiviral therapy
06	**Serum aminotransferase (ALT/AST) < 80 U/L**

Exclusion criteria

01	Co-infection with HCV or HIV
02	Follow-up duration less than six months or started AVT within six months
03	HCC detected within six months
04	Presence of other malignant tumor

Sinn DH, Paik SW et al., Gut N Liver 2016; Accepted article

Baseline characteristics

Characteristics	Derivation (n = 971)	No HCC (n = 945)	HCC (n = 26)	P value
Age (years, mean ± S.D)	42.6 ± 10.6	42.4 ± 10.5	51.4 ± 10.8	<0.001
Male (n, %)	564 (58.1)	544 (57.6)	20 (76.9)	0.048
HBeAg positive (n, %)	547 (56.3)	535 (56.6)	12 (46.2)	0.28
HBV DNA levels ()	5.95 ± 1.84	5.96 ± 1.85	5.74 ± 1.27	0.55
ALT (U/L, median, quartile)	34 (23-49)	34 (23-49)	37 (26-52)	0.28
AST (U/L, median, quartile)	29 (23-37)	29 (23-37)	31 (26-38)	0.076
Platelet (X 103/L, median, quartile)	205 (182-238)	206 (183-239)	186 (170-214)	0.023
REACH-B score (median, quartile)	10 (8-11)	10 (8-11)	12 (10-13)	<0.001
FIB-4 score	1.02 (0.72-1.40)	1.01 (0.71-1.38)	1.57 (1.22-1.87)	<0.001

Sinn DH, Paik SW et al., Gut N Liver 2016; Accepted article

Treatment criteria for CHB

Liver disease severity	Liver society	HBV DNA, IU/mL	ALT
Chronic hepatitis	EASL, 2012	≥ 2,000	≥ ULN
	AASLD, 2015	≥ 20,000 (e+), ≥ 2,000 (e-)	≥ 2 X ULN
	KASL, 2015	≥ 20,000 (e+), ≥ 2,000 (e-)	≥ 2 X ULN

EASL 은 간수치가 ULN만 넘어도 치료하라고 권고하고 있음.
AASLD는 50세 넘으면 Biopsy를 고려하라고 되어 있음

AUROC Comparison between risk scores

Year	Age	ALT
1	79.4 (66.1-92.7)	41.8 (36.0-47.5)
2	73.2 (59.6-86.8)	65.4 (52.3-78.4)
3	73.9 (61.5-86.2)	66.6 (54.7-78.3)
4	72.8 (60.1-85.3)	69.9 (59.8-80.0)
5	71.8 (58.4-85.2)	76.6 (68.4-84.7)
6	65.6 (49.6-81.5)	74.8 (65.0-84.5)

나이와 ALT가 간암의 발생과 연관은 있으나 AUROC가 41.8% - 76.6% (ALT), 65.5%-79.4% (나이) 정도의 AUROCS로 충분하지 않음

Sinn DH, Paik SW et al., Gut N Liver 2016; Accepted article

Risk factor for HCC development

	Model 1		Model 2		Model 3	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Log (HBV DNA)	1.10 (0.94-1.29)	0.21	**27.6 (7.43-102.7)**	**<0.001**	**18.7 (5.51-63.9)**	**<0.001**
Log (HBVDNA)^2	-	-	**0.88 (0.84-0.93)**	**<0.001**	**0.90 (0.86-0.94)**	**<0.001**
Age (year)	**1.09 (1.04-1.13)**	**<0.001**	**1.09 (1.04-1.14)**	**<0.001**	**1.07 (1.03-1.10)**	**<0.001**
Female	**0.37 (0.14-0.94)**	**0.038**	**0.37 (0.14-0.96)**	**0.042**	**0.28 (0.11-0.70)**	**0.006**
HBeAg (+)	0.74 (0.20-2.69)	0.65	0.91 (0.36-2.28)	0.84		
ALT (/IU/ml)	1.01 (0.99-1.02)	0.16	**1.02 (1.00-1.04)**	**0.022**		
AST (/IU/ml)	0.99 (0.96-1.03)	0.94	0.96 (0.92-1.01)	0.13		
Platelet (/X 10^3/L)	0.99 (0.97-1.00)	0.099	0.99 (0.98-1.00)	0.25		
Elevated ALT*	0.71 (0.27-1.89)	0.50	0.38 (0.13-1.10)	0.075		

Sinn DH, Paik SW et al., Gut N Liver 2016; Accepted article

D^2AS risk model for HCC

D^2AS model

2.9325 * log (HBV DNA IU/mL)

– 0.10527 * log(HBV DNA IU/mL)^2

+ 0.07013 * age (years)

+ -1.27223 * (2 if female, 1 if male)

D^2AS Risk score

(D^2AS model value – 15)/5*2

Sinn DH, Paik SW et al., Gut N Liver 2016; Accepted article

Comparison between risk scores

Year	D^2AS score	Age	ALT	HBV DNA	REACH-B	FIB-4
1	70.0 (54.8-84.9)	79.4 (66.1-92.7)*	41.8 (36.0-47.5)*	53.0 (15.4-90.6)	72.3 (60.0-84.4)	68.8 (32.2-99.9)
2	87.8 (79.9-95.7)	73.2 (59.6-86.8)*	65.4 (52.3-78.4)*	53.6 (43.1-64.1)*	78.6 (66.3-90.8)	74.5 (59.8-89.1)*
3	89.5 (82.3-96.6)	73.9 (61.5-86.2)*	66.6 (54.7-78.3)*	55.9 (46.4-65.3)*	81.4 (70.3-92.4)	75.9 (62.2-89.6)*
4	88.4 (81.7-94.9)	72.8 (60.1-85.3)*	69.9 (59.8-80.0)*	55.5 (47.6-63.3)*	75.0 (59.5-90.3)*	75.0 (64.3-85.6)*
5	88.4 (81.2-95.5)	71.8 (58.4-85.2)*	76.6 (68.4-84.7)*	55.6 (48.4-62.7)*	81.2 (70.7-91.6)	70.2 (56.2-84.1)*
6	88.2 (81.5-94.8)	65.6 (49.6-81.5)*	74.8 (65.0-84.5)*	60.4 (53.0-67.7)*	78.2 (67.2-89.1)*	64.1 (51.0-77.0)*

Sinn DH, Paik SW et al., Gut N Liver 2016; Accepted article

Performance of D²AS risk score

Derivation (n = 971)

Time	HCC	Survivors	Censored	AUROC (95% CI)
1 year	3	886	82	70.0 (54.8-84.9)
2 year	10	727	234	87.8 (79.9-95.7)
3 year	11	584	376	89.5 (82.3-96.6)
4 year	13	460	498	88.4 (81.7-94.9)
5 year	19	331	621	88.4 (81.2-95.5)
6 year	21	229	721	88.2 (81.5-94.8)

Validation (n = 507)

Time	HCC	Survivors	Censored	AUROC (95% CI)
1 year	3	463	41	95.1 (90.8-99.4)
2 year	7	420	80	94.2 (90.1-98.4)
3 year	11	382	114	88.9 (79.6-98.3)
4 year	13	353	141	88.0 (79.8-96.2)
5 year	13	265	229	87.6 (78.9-96.3)
6 year	15	127	365	77.8 (66.3-89.2)

Sinn DH, Paik SW et al., Gut N Liver 2016; Accepted article

Risk of HCC according to D²AS score

	Derivation				Validation			
Risk group by	Very low	Low	Intermediate	High	Very low	Low	Intermediate	High
D²AS score	< 1.0	1.0-1.9	2.0-2.5	≥ 2.5	< 1.0	1.0-1.9	2.0-2.5	≥ 2.5
Number	48	537	246	140	38	268	106	92
Risk score	0.9 ± 0.1	1.6 ± 0.3	2.2 ± 0.1	2.8 ± 0.2	0.8 ± 0.2	1.5 ± 0.3	2.2 ± 0.1	2.8 ± 0.2
HCC, n (%)	0 (0.0%)	3 (0.6%)	6 (2.4%)	17 (12.1%)	0 (0.0%)	1 (0.4%)	2 (1.8 %)	12 (13.0%)
Incidence								
3 years	0	0.2	0.9	7.3	0	0.5	0	12.5
5 years	0	0.7	2.7	17.8	0	0.5	1.1	13.8

Sinn DH, Paik SW et al., Gut N Liver 2016; Accepted article

Don’t rely too much on ALT levels

01 Minor, but significant proportion of patients developed HCC in patients with elevated HBV DNA levels and normal or mildly increased ALT levels.

02 The D^2AS risk score can play a valuable role in risk stratification, and may be useful to guide clinical decisions for enhanced surveillance or treatment to reduce HCC risk in this population.

HCC risk score in index patients

48/M

- B형간염
- HBeAg+
- HBV DNA = 2,090,000 IU/mL
- AST/ALT = 38/26
- US: chronic liver disease

D^2AS score

3.0

(high risk,

14 ~ 18% at 5 -years)

Take Home message

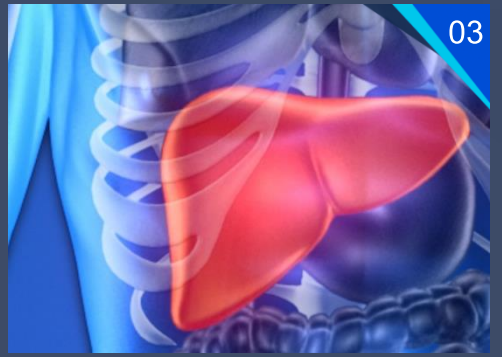
01 HBV DNA 농도가 높은 사람들은 AST/ALT가 정상 범위여도 주위가 필요한 분들이 있습니다.

02 D^2AS model과 같은 Risk model들을 임상결정에 보다 적극적으로 활용해 보세요.

What is option?

Observation

Biopsy



Treatment

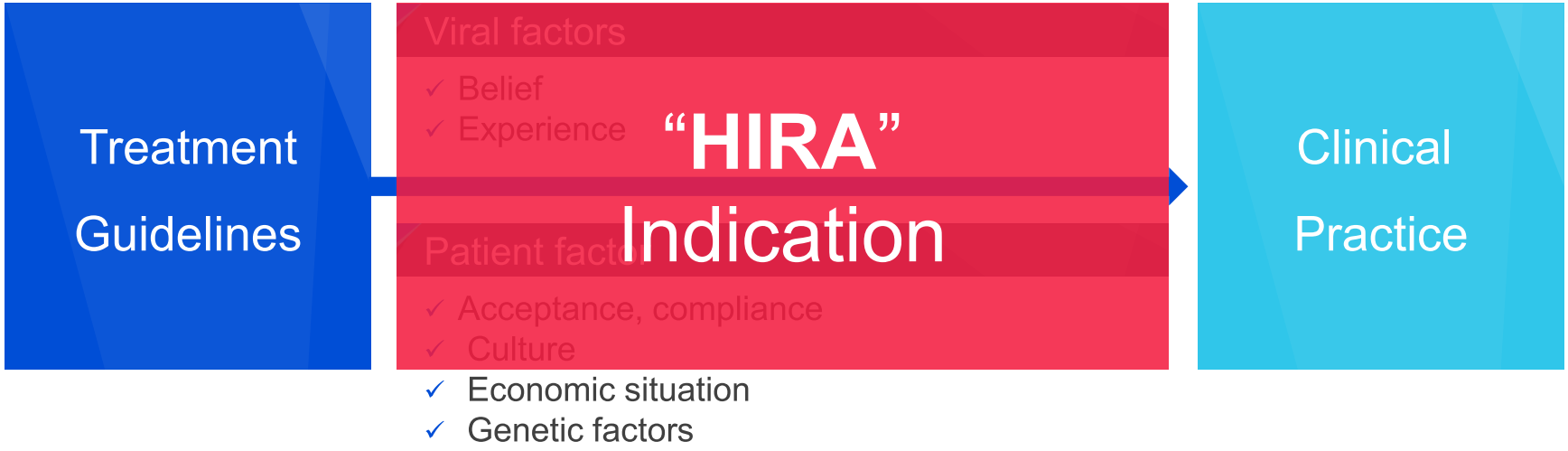
Personal indication

Determine severity of liver disease and CHB phase

1 Hepatitis	2 Compensated cirrhosis	3 Decompensated cirrhosis
ALT 상승 자연적으로 면역조절기로 갈 가능성을 평가 ALT 정상 Risk model로 위험도 평가	보험만족시 바로 치료시작 (비보험치료 적극 고려)	바로 치료시작

Ideal situation

Real life situation



HIRA indication

HIRA (Health Insurance Review and Assessment *Service*)

HBe + hepatitis	ALT ≥ 80, DNA ≥ 20,000 IU/ml
HBe – hepatitis	ALT ≥ 80, DNA ≥ 2,000 IU/ml
Cirrhosis	Any ALT, DNA ≥ 2,000 IU/ml
Decompensated cirrhosis, HCC	Any ALT, DNA detectable

Thank you

for your attention

SAMSUNG MEDICAL CENTER

SUNG KYUN KWAN UNIVERSITY (SKKU)